Abstract

Title

A study to assess utilisation and safety of Glycopyrronium Bromide 1mg/5ml Oral Solution as licensed for symptomatic treatment of severe sialorrhoea in children and adolescents aged 3 years and older with chronic neurological disorders in the UK.

Keywords

Glycopyrronium Bromide, Sialorrhoea, Drooling

Rationale and background

Glycopyrronium bromide 1mg/5ml Oral Solution, a synthetic muscarinic anticholinergic, is licensed for the symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged three years and older with chronic neurological disorders. This post-authorisation safety study (PASS) is being carried out as part of the Risk Management Plan for Glycopyrronium Bromide 1mg/5ml Oral Solution.

Research question and objectives

The primary objective is to describe the utilisation of Glycopyrronium Bromide 1mg/5ml Oral Solution in the UK in patients <18 years, including describing off-label use in patients aged below three years and/or patients with mild to moderate sialorrhoea. Additionally, the primary objective includes quantifying the follow up consultations in secondary and/or primary care.

The secondary objectives are to examine safety in long-term use (as defined by >24 weeks), including the incidence of important identified and potential risks within the first 12 months after starting treatment. The exploratory objective aims to quantify the provision of educational material to parents and carers.

Study design

A non-interventional prospective cohort study.

Setting

Patients were recruited in secondary care sites across the UK; 14 sites participated. Any patient aged <18 years prescribed Glycopyrronium Bromide 1mg/5ml Oral Solution within six months prior to enrolment, for an indication of sialorrhea, was eligible to participate.

Subjects and study size, including dropouts

Eight of the 14 sites recruited 18 eligible patients. One patient who was initially eligible became ineligible with further information provided from the GP, resulting in a total of 17 eligible patients contributing to the final cohort.

Variables and data sources

Data was collected on Glycopyrronium Bromide 1mg/5ml Oral Solution start dose, indication for prescribing, past medical history, adverse events experienced, concomitant medications, treatment changes, follow up consultations, and receipt and use of educational material.

Data was collected at baseline and at three monthly intervals thereafter from secondary care healthcare professionals. There was an optional contribution to primary data collection from the patient or their parent, guardian or carer at six and twelve months, and data collection from the patient's GP at twelve months.

Results

Of the 17 patients participating, data were collected from the secondary care team for all patients. Consent for primary data collection was provided for 13 of the 17 patients (76.5% of cohort); only from two of these patients (11.8% of cohort), primary data questionnaires were returned. For 11 of the 17 patients (64.7% of cohort), only GP collected data was received.

In the study, there were more females (58.8% of cohort) than males (41.2% of cohort). The median (IQR) age for the total cohort was 5 (3, 7) years. Less than five patients (<30% of cohort) were aged less than three years at index, and n<5 patients (<30% of cohort) had moderate drooling; both groups corresponding to off-label use. The most frequent starting dose was 3ml three times daily (<30% of cohort). Seven patients (42.4% of cohort) were started on Dose level 1 for their weight category (ranging from 1.5ml if weight is 13 to <18kg to 5ml if weight is ≥48kg), in line with prescribing recommendations. Less than five patients (<30% of cohort) had a dose lower than the minimum dose for their weight category. No patient had a dose higher than recommended for their weight category.

Median (IQR) cohort exposure time up to 12 months was 356 (120, 365) days. Of the 17 patients, eight patients (47.1% of cohort) had a cohort exposure of at least 12 months. To support the secondary objective of assessing safety in long term use (defined as >24 weeks), 12 of the 17 patients (70.6% of cohort) had cohort exposure beyond 24 weeks, thereby contributing to the evaluation of longer-term safety.

During the 12-month observation period, nine patients (75.0% of cohort) experienced at least one targeted event (which are specifically listed in the HCP checklist). The event of constipation was most frequently reported (35.3% of cohort), followed by pneumonia (<30% of cohort). Urinary retention, central nervous system effects, overheating and allergic reaction events were each reported in small counts (<30% of cohort). Less than five patients died during the course of the study (<30% of cohort); all patients experienced respiratory manifestations against a background of complex comorbidities that were likely contributory risk factors.

In relation to treatment changes, seven patients (41.2% of cohort) had a dose increase, and n<5 patients were reported to have a dose and/or frequency decrease (<30% of cohort). Seven patients (41.2% of cohort) discontinued Glycopyrronium Bromide within 12 months, with n<5 of these patients reporting an anticholinergic adverse event as the reason for stopping.

A HCP checklist was received by the HCP from the Marketing Authorisation Holder (MAH) for five patients (29.4% of cohort) and a reminder card for caregiver was received by the HCP for four patients (23.5% of cohort). A secondary care follow up consultation was reported for 15 of the 17 patients (88.2% of cohort) and a follow up consultation in primary care for 10 patients (58.8% of cohort).

Discussion

Most patients enrolled in this study were prescribed Glycopyrronium Bromide according to the licensed indication: use in patients three years or older for severe drooling. Nevertheless, off-label use was observed in approximately one-third of the cohort. Specifically, n<5 patients were prescribed the product under the age of three years, and an additional n<5 patients had a moderate drooling severity. Whilst a high proportion of patients started Glycopyrronium Bromide according to the dosing schedule, patients were also prescribed a dose which fell between specified Dose levels or less than the recommended Dose level 1 for the patient's weight. Two-thirds of patients experienced at least one adverse event listed as an important identified or potential risk. Constipation was the most frequent experienced event, followed by pneumonia. Longer term safety data (>24 weeks) were available for 12 of the 17 patients. Overall, the reported adverse events are consistent with the established safety profile of the product. However, some of these adverse events were serious, either resulting in hospital admission or serious by nature of the adverse event. Deaths were reported during the study period (n<5). The confirmed number of receipt of educational materials was low for HCPs taking part in the study. Due to challenges in patient recruitment leading to a limited sample

size, it is not feasible to draw definitive conclusions regarding utilisation, safety, or the effectiveness of the product's additional risk minimisation measures.